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Unexpected low prevalence of atrial fibrillation in cryptogenic ischemic stroke: a prospective study

Fanny Dion · Denis Saudeau · Isabelle Bonnaud · Patrick Friocourt · Armel Bonneau · Philippe Poret · Bruno Giraudeau · Sandra Régina · Laurent Fauchier · Dominique Babuty

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Abstract
Purpose Ischemic stroke is a frequent pathology with high rate of recurrence and significant morbidity and mortality. There are several causes of stroke, affecting prognosis, outcomes, and management, but in many cases, the etiology remains undetermined. We hypothesized that atrial fibrillation was involved in this pathology but underdiagnosed by standard methods. The aim of the study was to determine the incidence of atrial fibrillation in cryptogenic ischemic stroke by using continuous monitoring of the heart rate over several months. The secondary objective was to test the value of atrial vulnerability assessment in predicting spontaneous atrial fibrillation.

Methods and results We prospectively enrolled 24 patients under 75 years of age, 15 men and 9 women of mean age 49 years, who within the last 4 months had experienced cryptogenic stroke diagnosed by clinical presentation and brain imaging and presumed to be of cardioembolic mechanism. All causes of stroke were excluded by normal 12-lead ECG, 24-h Holter monitoring, echocardiography, cervical Doppler, hematological, and inflammatory tests. All patients underwent electrophysiological study. Of the patients, 37.5% had latent atrial vulnerability, and 33.3% had inducible sustained arrhythmia. Patients were secondarily implanted with an implantable loop recorder to look for spontaneous atrial fibrillation over a mean follow-up interval of

F. Dion · L. Fauchier · D. Babuty (✉)
Service de Cardiologie B, pôle Cœur, Thorax, Vaisseaux, hôpital Trousseau, Tours University,
CHRU de Tours,
37044 Tours Cedex 9, France
e-mail: d.babuty@chu-tours.fr

D. Saudeau · I. Bonnaud
Service de Neurologie, hôpital Bretonneau, Tours University,
CHRU de Tours,
37044 Tours Cedex 9, France

P. Friocourt
Service de Médecine interne—Neurologie,
Centre Hospitalier de Blois,
Mail Pierre Charlot,
41016 Blois Cedex, France

A. Bonneau
Service de Médecine A—Cardiologie,
Centre hospitalier de Châteauroux,
216, avenue de Verdun BP 585,
36019 Châteauroux Cedex, France

P. Poret
Cardiologie, Clinique de Pontlieue,
19 place Adrien Tironneau,
72100 Le Mans, France

B. Giraudeau
Centre d'Investigation Clinique INSERM 202,
Tours University,
CHRU de Tours,
37044 Tours Cedex 9, France

S. Régina
Laboratoire d'Hématologie, Hémostase, hôpital Trousseau,
Tours University,
CHRU de Tours,
37044 Tours Cedex 9, France

14.5 months. No sustained arrhythmia was found. Only one patient had non-significant episodes of atrial fibrillation.
Conclusion In this study, symptomatic atrial fibrillation or AF with fast ventricular rate has not been demonstrated by the implantable loop recorder in patients under 75 years with unexplained cerebral ischemia. The use of this device should not be generalized in the systematic evaluation of these patients. In addition, this study attests that the assessment of atrial vulnerability is poor at predicting spontaneous arrhythmia in such patients.

Keywords Atrial fibrillation · Stroke · Cardioembolic · Atrial vulnerability · Implantable loop recorder

1 Introduction

Ischemic stroke (IS) is a frequent pathology whose incidence sharply increases with age, 0.1/1,000 inhabitants per year below the age of 45 and up to 10/1,000 over 75 years of age in France [1]. It is the third cause of death and is responsible for 50% of disabling conditions in survivors [2] in industrialized countries. The causes are various, but events of undetermined etiology are frequent [3]. We suggested that a significant proportion of these unexplained strokes or transient ischemic attacks (TIA) could be due to undiagnosed atrial fibrillation (AF). AF is a common cause of embolism, but it can be difficult to identify due to asymptomatic or paroxysmal episodes [4, 5]. Some authors have advocated studying the atrial vulnerability (AV) to arrhythmias to explain the mechanism of cryptogenic IS [6, 7]. In the presence of a low atrial vulnerability index or induction of AF, oral anticoagulation and antiarrhythmic therapy were recommended by these same authors, but the predictive value of this electrophysiological method for spontaneous AF remains controversial [8, 9]. We therefore aimed to document spontaneous AF in a population of patients with unexplained IS/TIA, using invasive continuous cardiac monitoring by means of an implantable loop recorder (ILR). This device, widely used for diagnosis of unexplained syncope [10], has proven effective in detecting paroxysmal arrhythmias [11, 12]. We also wanted to correlate the results of continuous electrocardiogram monitoring with those of AV electrophysiological studies in order to test the value of this method for predicting spontaneous AF.

2 Patients and methods

This is a prospective multicenter study whose aim was to determine the prevalence of AF in patients under 75 years of age with a history of IS or TIA of undetermined cause after complete evaluation.

2.1 Patient enrollment

The enrollment took place in the cardiology or neurology units of four hospitals in France. Patients were to be between 18 and 75 years old, have a history of cerebral ischemia within 4 months before inclusion, and have recovered neurological status allowing good autonomy (Rankin score between 0 and 2 at inclusion [13]). The neurological features of each patient were reviewed by the referent neurologist of the study, who validated the diagnosis of IS/TIA from anamnesis, clinical presentation, and the results of brain imaging. All patients underwent at least cerebral CT or MRI, or both, depending on the equipment of the recruiting centre. Cerebral hemorrhage was excluded. Undetermined origin was ascertained by negative evaluation requiring ancillary tests performed in all patients to exclude the following conditions:

- Ipsilateral carotid atherosclerotic stenosis >70%, vertebral or carotid dissection with cervical Doppler-echography or angio-MR.
- Documented atrial fibrillation, with a 12-lead electrocardiogram and 24-h Holter monitoring.
- Intracardiac thrombus or any other cause of cardiac embolism, with transthoracic (n=24/24) and transesophageal echocardiography (n=22/24).
- Vascular malformation, by means of cerebral CT, MRI or angio-MRI if necessary.
- Hypercoagulable states, hematological disorders, and inflammatory diseases, with biological tests carried out at least 2 months after stroke: prothrombin ratio, activated partial thromboplastin time, C and S proteins, antithrombin, mutation in Factor V Leiden gene, circulating anticoagulants, antiphospholipid and anti-ß2gp1 antibodies, homocysteinemia, erythrocyte sedimentation rate, and C-reactive protein.

A history of documented cardiac arrhythmias and ineffectively controlled pre-stroke hypertension (defined by systolic blood pressure >140 mmHg or diastolic >90 mmHg) were also exclusion criteria.

Informed consent was signed by all patients before inclusion.

The study protocol resulted from a regional 2003 Hospital Program of Clinical Research promoted by the University Hospital of Tours and received approval from the Institutional Ethics Committee (CCPPRB of Tours) on June 29, 2004.

2.2 Study of atrial vulnerability

The electrophysiological study was performed using low-molecular-weight heparin for effective anticoagulation. Two quadripolar electrode catheters (10-mm interelectrode

distance, USCI, Bard) were placed in the right cardiac cavities via catheterization of the right femoral vein under local anesthesia. One quadripolar electrode was positioned in the high right atrium (HRA) in the sinus node area; the other one was placed in the low right atrium (LRA) near the atrioventricular node. Pacing was performed with a programmable stimulator (Biotronik UHS, Germany) which delivered rectangular pulses of 2-ms duration at twice the diastolic threshold. The study was carried out in three stages:

- Measurement of basic conduction intervals and determination of the Wenckebach point of the atrioventricular node.
- Determination of the right atrium refractory periods (RP) and the duration of the atrial electrogram. RPs were determined by means of an extrastimulus (S2) delivered at three different constant pacing rates 100, 120, 150 bpm. Effective RP was defined as the longest attainable S1–S2 interval that did not produce an atrial electrogram. Finally, we measured the duration of the atrial electrogram (A2) following S2 at a pacing rate of 100 bpm. Latent vulnerability index (LVI) was defined as the ratio between high right atrium effective refractory period (ERP) and A2 duration at a pacing rate of 100 bpm [7, 14].
- Assessment of the inducibility of atrial arrhythmia was performed by programmed atrial stimulation with up to three extrastimuli (S2, S3, S4) at constant pacing rates of 100, 120, and 150 bpm at two different stimulation sites: HRA and LRA.

Latent atrial vulnerability was defined as LVI <2.5, and atrial inducibility as induction of sustained atrial arrhythmia lasting >60 s [7, 14].

2.3 Implantation of Holter monitor

The ILR (Medtronic™ Reveal® Plus ILR 9526, Medtronic Inc., Minneapolis, USA) is a small single-use device fitted with two sensing electrodes. It can record the heartbeat loop for 14 months. When interrogated transcutaneously, it can return recorded rhythmic events. The ILR was implanted subcutaneously under local anesthesia and antibiotic prophylaxis in the left pectoral region. The device was programmed similarly for all patients before their discharge:

- Semi-automatic activation mode.
- Recording of 13 automatic events and 1 event by patient activation. Patients were provided with an activator at the time of device implantation.
- The criteria for automatic recording were bradycardia <30 bpm or pause >3 s, tachycardia >165 bpm for more than 32 complexes.

Patients were instructed to activate the device in case of palpitations, syncope, or recurrence of IS/TIA.

2.4 Treatment

All patients received antiplatelet therapy, aspirin 300 mg/day, or clopidogrel 75 mg/day.

2.5 Patient follow-up

Patients underwent examination and 12-lead ECG every 4 months, performed by the investigator of the recruiting hospital. Interrogation of the ILR was carried out at each visit and stored for review by the principal investigator. AF was considered to have occurred when normal sinus rhythm was replaced by irregular tachycardia lasting more than 30 s with no visible P wave or with unorganized F wavelets of AF. In this case, antiarrhythmic therapy was prescribed according to the habitual procedure of each investigator, and antiplatelet therapy was replaced by oral anticoagulation treatment with a target International Normalized Ratio (INR) between two and three. In the event of a serious issue (recurrence of stroke, syncope, death), the nearest investigator hospital was contacted for interrogation of the ILR. The study ended for a patient when sustained AF was documented by the monitor or after the monitoring period of 14 months with the device's explantation (end of battery life defined by the manufacturer of the Reveal Plus® ILR 9526).

3 Results

Twenty-four patients were included, 15 men and 9 women, from 19 to 74 years old, mean age 48.8±13.6 years. The subjects' characteristics are summarized in Table 1. Although 50 patients were provided, inclusions were stopped prematurely because of negative results.

Table 1 Characteristics of subjects (n=24)

Male *n* (%)	15 (62.5)
Age (years) (mean±SD)	49±13.6
<50 years *n* (%)	14 (58.3)
Diabetes mellitus	0
Hypertension *n* (%)	7 (29.2)
Dyslipidemia *n* (%)	8 (33.3)
Active tobacco use *n* (%)	10 (41.7)
Overweight (BMI>27.5) *n* (%)	4 (16.7)
Vascular ischemic hereditary *n* (%)	5 (20.8)

Table 2 Neurological features: topography of cerebral infarcts (n=24)

Topography of infarcts	Number	Percentage
Middle cerebral artery (MCA) territory	20	83.3
Superficial MCA	14	58.3
Deep MCA	3	12.5
Global MCA	3	12.5
Vertebrobasilar territory	7	29.2
Posterior cerebral artery territory	3	12.5
Cerebellum	4	16.7
Multiple lesions	8	33.3
Bilateral	5	20.8

3.1 Neurological features

Of the 24 enrolled patients, 3 (12.5%) experienced TIA with symptoms lasting less than 1 h (and normal brain MRI), and 21 (87.5%) experienced cerebral infarction; one of them remained with neurological sequelae (Rankin score=2), symptoms were fully reversible in all the others. The clinical presentation consisted of lateralized motor deficit or aphasia in 75% of the cases, with or without sensory symptoms. There was one case of isolated retinal event. All patients underwent at least one brain imaging, cerebral CT (n=17) or MRI (n=15) or both (n=8), and four patients had an angio-MRI performed. The topography of cerebral ischemia is summarized in Table 2. The most common types of infarcts were superficial middle cerebral artery territory infarcts (58.3%). One in three patients showed at least two concomitant ischemic locations, lesions were bilateral in 20.8% of cases. Brain MRI revealed images of past infarcts in four cases (26.7%).

3.2 Electrophysiological study

The results are shown in Table 3. We observed 18 patients with supraventricular arrhythmias, 15 AF, 1 common flutter, and 2 other atrial tachycardias. Eight of these, termed “inducible” patients, experienced sustained arrhythmia, lasting more than 60 s. The LVI was calculated whenever possible with the formula described above. It could not be calculated in four cases because of the impossibility of measuring RP or A2 duration due to early onset of sustained arrhythmia. Latent AV was found in nine patients (37.5%), among whom, three were inducible.

3.3 Implantable ECG monitor

The mean time lapse from cerebral accident to initiation of cardiac rhythm monitoring, i.e., implantation of the ILR, was 3±1.1 months. The mean monitoring duration was 14.5 months. There was no loss of follow-up. There was no recurrence of stroke, no episode of syncope or palpitation was reported, and all electrocardiograms were in sinus rhythm. Through ILR interrogation, we found short AF episodes <30 s in one patient (4.2%), detected by automatic record, with a ventricular rate exceeding 200 bpm. This patient was not inducible through programmed atrial stimulation despite a positive latent vulnerability (LVI=1.5). No significant AF episode or any other sustained arrhythmia was identified, either in inducible patients or in the others. Moreover, no significant sinus pause or sinus bradycardia was observed that could have led to a diagnosis of bradycardia–tachycardia syndrome.

Table 3 Electrophysiological study results (n=24)

	Mean±SD	Min	Max	Number (%)
AH interval (ms)	83±22.4	15	125	
HV interval (ms)	43±9.38	30	65	
Wenckebach point of AV node (bpm)	162±35.2	110	230	
HRA ERP (ms)	234±37.1	180	290	
A2 duration (ms)	85±26.4	50	140	
LVI (n=20)	2.9±1.02	1.5	5.6	
LVI<2.5				9 (37.5)
Inducibility of atrial arrhythmia (including AF, flutter, and other atrial tachycardias)				18 (75.0)
0–30 s				8 (33.3)
30–59 s				2 (8.3)
1–5 min				5 (20.8)
>5 min				3 (12.5)

4 Discussion

4.1 Atrial fibrillation and stroke

Because of the high recurrence rate of ischemic cerebral accidents, secondary prevention after a first-ever event is essential. Despite an extensive evaluation, no determined etiology is found in one third to half of all cases, especially in young subjects [15]. It is currently estimated that 30% of IS have a cardioembolic substrate, about half of which are due to AF [3]. AF is a very common arrhythmia whose prevalence increases with age up to 10% after the age of 75 versus 0.4% in the general population [16]. Arterial embolism is a frequent complication of AF, with a risk of 5% to 10% per year, especially in subjects with cardiovascular risk factors (hypertension, diabetes, heart failure) [17, 18]. Identifying a potential cardiac source of embolism is of critical importance in the etiological workup of IS because of therapeutic and prognostic implications. Epidemiological studies have shown a poorer prognosis for IS/TIA of cardioembolic origin than from other causes, especially those due to AF [3, 19, 20]. If AF is identified as the cause of a first-ever cerebral infarction, anticoagulation therapy significantly reduces the recurrence rate as compared with antiplatelet therapy and dramatically improves these patients' prognosis [17, 21–23]. Unfortunately, AF is difficult to detect. The yield is low for 12-lead ECGs, as well as for 24- to 72-h Holter monitoring (2% to 5%) [24, 25]. Preliminary studies suggested that extending the duration of heart rate monitoring would increase the probability of detecting paroxysmal AF [25–27]. The ILR offers the benefit of continuously monitoring cardiac rhythm over several months.

In our study, cerebral ischemic accidents were suspected to be of cardioembolic mechanism, as evidenced by the frequency of multiple, especially bilateral lesions. The exclusion of uncontrolled pre-stroke hypertension limited possible confusion with lacunar events. Nevertheless, among the 24 enrolled patients, AF was detected as a potential cause of stroke in only one patient. In a recent study by Tayal et al. [28] on patients with cryptogenic IS/TIA, the authors found a higher detection rate of AF using 21-day monitoring with mobile cardiac outpatient telemetry, 5.3% of AF >30 s and 23% of short episodes <30 s. We can assume that the difference is due to patient selection and time of initiation of the monitoring. In the Tayal study, the patients were at higher risk of AF because they were older (mean age 66±11 versus 49±13 years in our study), and the prevalence of diabetes was high. Age and diabetes mellitus are well-known risk factors for AF [16, 29]. It is to be noticed that diabetics were absent from our population. In the Tayal study, rhythm monitoring after index event was initiated earlier than in ours (mean 20 days versus 3 months). In their work, the majority of AF were diagnosed within the first days of monitoring (mean 7 days, range 2–19). However, early transient AF has been reported after acute stroke only as a consequence of the stroke [30], which led us purposely to choose to delay the initiation of monitoring in order to avoid confusion as to the responsibility of the stroke for the onset of paroxysmal arrhythmia.

4.2 Atrial vulnerability

The aim of the AV study was to identify subjects with a high risk of atrial arrhythmia. It has been shown that patients with documented AF more often have a low LVI and are more easily inducible than patients without AF [8, 15]. The predictive value of these findings has been studied in different clinical situations. Some authors have described similar electrophysiological abnormalities in patients with paroxysmal AF and in patients with unexplained ischemic stroke [8, 31]. However, the correlation between the presence of an arrhythmogenic substrate and the occurrence of spontaneous AF has not been proven. In previous series, the percentage of inducible sustained AF in patients with cryptogenic IS was 50% to 65% [6, 8]. We also found a high rate of inducible sustained atrial arrhythmias (33.3%) and a high rate of latent AV (37.5%), whereas no spontaneous sustained asymptomatic AF or AF with fast ventricular response was documented over a period of 14 months. Moreover, the only patient who experienced short episodes of spontaneous AF was not inducible by programmed atrial stimulation. For the first time, continuous monitoring in a prospective study has made it possible to confirm the irrelevance of electrophysiological study in the etiological workup of IS/TIA, because neither low LVI nor atrial arrhythmia inducibility was predictive of spontaneous AF.

4.3 Limitations of the study

This study has some limitations. Firstly, the duration of the study was shortened by the device's limited battery life. Rhythm monitoring was thus limited to 14 months, which is brief compared to the period of stroke recurrences. As epidemiological data in the literature reveal that the risk of recurrent stroke is high in the early phase after a first-ever event and remains high for several years thereafter [19, 32, 33], there is little prospect that the new generation of ILR with a prolonged battery life (more than 36 months) would be more informative. A second limitation arose from the drawbacks of the ILR device itself. The algorithm required 32 consecutive beats at 165 bpm to recognize a rhythm disturbance as an AF episode. It was consequently programmed to record AF with rapid ventricular response, making it likely that a number of non-rapid episodes may have been missed. Regarding self-activation, previous

studies have showed the inability of some patients to operate loop recorders properly [11]. This was not a problem in our study because no triggering symptom was experienced resulting from patients' failure to activate. In the future, the ILR will be designed to record atrial activity more accurately in order to diagnose AF with lower ventricular response. The latest model of ILR (Reveal® XT, Medtronic Inc., Minneapolis, USA) seems to meet this objective, but the device is not yet available in France.

Finally, it might be objected that a major limitation lies in the limited size of the study, given the low number of 24 subjects included. Patients' inclusion was hampered by difficulties in getting them to accept the protocol, particularly because of the invasiveness of procedures. Inclusion was limited to 24 patients for reasons of ethical considerations and cost effectiveness on the grounds that the absence of sustained AF in this population made the diagnostic method uneconomical. We suspect that the efficacy of the method could be improved by applying it to a selected population at higher risk of AF, specifically including more diabetics and older patients.

5 Conclusion

This study suggests that symptomatic atrial fibrillation or AF with fast ventricular rate is not a frequent pathology in patients under the age of 75 with unexplained ischemic stroke. These results do not plead for generalizing the use of an implantable loop recorder in the systematic evaluation of these patients. Further studies are needed to test the efficacy and cost effectiveness of the method in a selected population with a higher risk of atrial fibrillation, using an updated device that more accurately diagnoses AF with low ventricular response. Finally, this study asserts that the electrophysiological study of atrial vulnerability is poor at predicting spontaneous atrial fibrillation after cryptogenic cerebral ischemia.

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Conflict of interest The authors have no conflict of interest.

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